

Altered Amygdala Connectivity Within the Social Brain in Schizophrenia

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Background: Impairments in social cognition have been described in schizophrenia and relate to core symptoms of the disorder. Social cognition is subserved by a network of brain regions, many of which have been implicated in schizophrenia. We hypothesized that deficits in connectivity between components of this social brain network may underlie the social cognition impairments seen in the disorder. **Methods:** We investigated brain activation and connectivity in a group of individuals with schizophrenia making social judgments of approachability from faces ($n = 20$), compared with a group of matched healthy volunteers ($n = 24$), using functional magnetic resonance imaging. Effective connectivity from the amygdala was estimated using the psychophysiological interaction approach. **Results:** While making approachability judgments, healthy participants recruited a network of social brain regions including amygdala, fusiform gyrus, cerebellum, and inferior frontal gyrus bilaterally and left medial prefrontal cortex. During the approachability task, healthy participants showed increased connectivity from the amygdala to the fusiform gyri, cerebellum, and left superior frontal cortex. In comparison to controls, individuals with schizophrenia overactivated the right middle frontal gyrus, superior frontal gyrus, and precuneus and had reduced connectivity between the amygdala and the insula cortex. **Discussion:** We report increased activation of frontal and medial parietal regions during social judgment in patients with schizophrenia, accompanied by decreased connectivity between the amygdala and insula. We suggest that the increased activation of frontal control systems and association cortex may reflect a compensatory mechanism for impaired connectivity of the amygdala with other parts of the social brain networks in schizophrenia.

Key words: fMRI/social cognition/approachability/psychosis/neural/psychophysiological interaction

Introduction

Schizophrenia is associated with significant impairments in social functioning,^{1,2} including difficulties in social decision-making.^{1,3–5} These have been shown to correlate with symptoms including paranoid and persecutory delusions^{4,6,7} and have been related to poor long-term outcome.^{8,9} However, the neural basis of impairments in social judgment and the relationship with symptoms of schizophrenia is not established.

Social cognition has been extensively studied in healthy individuals, and a distributed network supporting social function has been identified.^{1,10,11} Such studies have primarily used face stimuli because these encode a wide range of social information, including a person's identity and emotional state.^{10–12} One of the key brain regions associated with emotional aspects of face processing is the amygdala.^{10,11,13–15}

Amygdala damage has been shown to affect recognition of negative emotions from faces and social judgments related to threat, as well as judgments concerning approachability and trustworthiness.¹⁶ The pivotal role of the amygdala in emotion processing, along with its anatomical connections to multiple brain regions including the prefrontal cortex,^{17–19} insula,^{19,20} superior temporal cortex,¹⁹ fusiform,¹⁹ hippocampus,²¹ and motor and sensory regions²² supports the premise that the amygdala is a central hub in the social brain network.^{23,24}

Individuals with schizophrenia have significant difficulties in making social judgments from facial stimuli.^{2,3,25,26} Imaging studies have demonstrated structural and functional abnormalities in regions of the social brain including the amygdala, medial prefrontal cortex, superior temporal cortex, insula, and fusiform gyrus.^{26–28} The distributed nature of these abnormalities raises the possibility that alterations in connectivity within social brain networks might underlie the behavioral deficits in social function in the disorder.^{26,29}

Abnormal connectivity has been widely reported in schizophrenia and has long been hypothesized to represent a central mediator of illness.³⁰⁻³³ While increased functional connectivity has been shown in some studies,³⁴⁻³⁶ many have reported reduced connectivity between task relevant network nodes.^{34,37-42} Notably, reduced amygdala connectivity has been demonstrated during tests of facial identity and affect recognition,⁴³ as well as emotion processing.⁴⁴ Postmortem studies have highlighted cellular and molecular changes, including reduced dendritic arborization, which may underlie reduced connectivity in the disorder.^{45,46}

In this study, we investigated the neural basis for making approachability judgments from faces in people with schizophrenia and healthy controls. We hypothesized that people with schizophrenia would demonstrate differential activation within the social brain network, compared with the controls, while judging approachability. Additionally, based upon the strong indications of dysconnection in the disorder, we also hypothesized that there would be decreased effective connectivity between the amygdala and other social brain regions in patients.

Methods

Participants

Twenty-four patients meeting DSM-IV diagnostic criteria for schizophrenia took part in the study. Exclusion criteria were age under 18 or over 65, neurological disease, other psychiatric disorder, and dependence on alcohol or nonprescribed drugs. One participant was subsequently excluded from the analysis due to the presence of a benign cerebral cyst and 3 individuals due to failure to make any behavioral responses in the scanner.

The remaining 20 individuals in the patient participant group were all Caucasian, and all were treated with antipsychotic medication (16 with atypical antipsychotics) having a mean chlorpromazine equivalent dose of 494 mg (SD 367 mg).^{47,48} Symptoms were rated on day of scanning using the positive and negative syndrome scale (PANSS).⁴⁹ The mean PANSS total score was 22.7 (SD 5.1). The mean positive syndrome score was 12.3 (SD 4.5), with 15 out of the 20 individuals scoring 3 or greater, indicating mild or greater severity, on one or more positive syndrome items. The mean negative syndrome score was 15.8 (SD 4.2).

Additionally, 24 healthy control volunteers were recruited from the same communities as the patients themselves. All control participants were Caucasian, were right handed, and had the same exclusion criteria as the patients, with the additional exclusion of any family or personal history of schizophrenia or major psychiatric illness. Local ethics approval was obtained and all participants gave informed consent. Detailed demographics are shown in [table 1](#).

Table 1. Demographic Details for All Individuals in the Study

Group (Size)	Age (SD)	National Adult Reading Test (SD)	Gender, M:F
Patients (20)	37.5 (8.2)	111.6 (9.8)	12:8
Controls (24)	35.13 (9.7)	114.6 (6.5)	16:8

Note: No Significant differences were found between the groups.

Experimental Design

The functional magnetic resonance imaging (fMRI) task used was similar to our previous study.^{50,51} In brief, the task consisted of 3 conditions: approachability judgment, gender judgment, and rest. In the approachability condition, participants were presented with facial images and asked to rate the approachability of the faces by selecting one of the dichotomized choices presented (“very approachable” or “not approachable”). Judgments were considered to be “correct” if they agreed with previously determined ratings derived from a separate group of raters, given that such social decisions based on perceived facial image stimuli are usually highly consistent. In the gender condition, participants were asked to indicate the gender from the same facial images used in the approachability condition. Order of conditions were counterbalanced across participants. That is, one group of participants started with the approachability judgments followed by gender judgments, while the other group did the reverse. During rest blocks, participants were instructed to look at a fixation cross in the center of the screen. Thirty-six different faces were used (half male and half female). The task consisted of 2 runs of 6 blocks each. Each block was 25 seconds in duration, with 6 faces being presented for 3.5 seconds each, separated by 0.5 seconds interstimulus interval, with a 1-second task prompt at the start of the block. Further, there were rest blocks (12.5 seconds) between experimental blocks. Further details regarding the task design are described in the [online supplementary methods](#).

Image Acquisition and Analysis

Image acquisition and analysis is described in detail in the [online supplementary methods](#). Image analysis was conducted using Statistical Parametric Mapping-2 (SPM2) (www.fil.ion.ucl.ac.uk/spm). Contrast images were generated for each participant for the pairwise comparison of parameter estimates between the individual conditions (approachability greater than gender, approachability greater than baseline, and gender greater than baseline). We focused on the approachability greater than gender contrast for subsequent analysis, as the contrast of interest. These individual subject-level results were used in a random effect group analysis using a 2-sample *t* test.⁵² Co-ordinates of peak activation within each of

the significantly activated clusters in the contrast were reported, along with the corresponding P values at the corrected cluster level. A small volume correction (SVC) was used for the amygdala, using a bilateral amygdala mask generated derived from the WFU PickAtlas.⁵³

Connectivity Analysis

Psychophysiological interaction (PPI) models assess effective connectivity from a chosen seed region to each voxel in the whole brain, corresponding to changes in experimental conditions. For the PPI analysis, the psychological term was defined as the change of estimated brain activation between the experimental conditions of interest, or approachability greater than gender.

The physiological term was estimated as the first eigenvariate time series of the blood oxygen level dependent (BOLD) signal extracted from an anatomically defined seed volume of interest (VOI) for each individual subject. This term denotes the average BOLD signal weighted by the voxel significance using the VOI extraction function in SPM.⁵⁴ Hemodynamic deconvolution was performed on the extracted time series to remove the effects of the canonical hemodynamic response function (HRF).

The resulting time series were multiplied by the psychological variable and reconvolved with the HRF to obtain the PPI interaction term using the PPI SPM function.⁵⁵ The time series were not adjusted for any effects because confounds related to nuisance regressors were factored into the previous stages of data regression.

The psychological, physiological, and interaction terms were entered into each subject's general linear model, with the interaction term as the regressor of interest.⁵⁴ These individual subject-level results were used in a random effects group analysis using a 2-sample t test⁵² to derive the group level effects. Voxels showing a group difference in connectivity between the seed VOI and the rest of the brain were reported, with cluster-corrected P values.

The seed region was functionally localized on the basis of peak activation in control participants within a mask representing the amygdala, as defined using the WFU Pick Atlas⁵³ (peak co-ordinates = $-22, -8, -20$ for the left amygdala and $18, 2, -18$ for the right amygdala). The control group was used in order to represent nonpathological amygdala activation. The region of interest was defined as 6-mm radius sphere, based on the smoothing kernel, the size of the anatomical region, and previous similar studies.⁵⁶

Statistical Analysis

All statistical maps were thresholded at a level of $P < .005$ uncorrected, and regions were considered significant at $P < .05$, corrected for multiple comparisons using cluster-level correction in SPM. No extent threshold was applied.

Co-ordinates of peak activation within each significantly activated cluster were reported as an estimate of the difference in connectivity from the VOI, between the 2 groups, with the corrected cluster-level P values. All co-ordinates were reported using the Montreal Neurological Institute (MNI) convention. Images were overlaid onto standard brain in MNI space using Mango (<http://ric.uthscsa.edu/mango>). Maps represent T-statistic images thresholded equivalent to $P = .005$.

Correlation analysis was performed using bivariate correlations in SPSS to assess (a) whether the connectivity observed in patients was affected by antipsychotic medication dosage, following conversion to chlorpromazine equivalents^{47,48} and (b) to assess whether connectivity was related to symptoms. Connectivity was estimated as the first eigenvariate time series extracted from a sphere, radius 6mm, at the regions found to be significantly connected to the seed region in the above analysis. The PANSS total score and PANSS positive or PANSS negative symptoms were used for this analysis.

Results

Demographics

There were no significant differences between individuals with schizophrenia and healthy controls in terms of age ($F_{1,42} = 0.1, P = .1$), National Adult Reading Test intelligence quotient ($F_{1,42} = 0.0, P = .9$), or gender (Fisher's Exact Test, $P = 1.0$), as shown in [table 1](#).

Difference in Social Behavior Between Groups

Within-scanner behavioral measures of approachability and gender discrimination showed no significant differences between groups using a 2-sided t test (approachability judgments: $t(41) = -1.711, P = .095$; gender judgment: $t(41) = -0.564, P = .591$). Further, both groups demonstrated a high degree of accuracy for both approachability (patients 80% correct, SD 13.1%; control participants 87% correct, SD 13.1%) and gender (patients 94% correct, SD 14%; control participants 95% correct, SD 13.7%).

BOLD Activation in Control Participants and Patients

While making approachability compared with gender judgments, healthy participants significantly activated a large cluster with a peak in the left medial prefrontal cortex ($P_{\text{corr}} < 0.001, K_E = 2652, T = 5.57$, peak co-ordinates = $-8, 40, 52$), a cluster with peak in the right inferior frontal gyrus ($P_{\text{corr}} = 0.007, K_E = 978, T = 4.69$, peak co-ordinates = $56, 24, 0$), a cluster with peak in the left inferior frontal gyrus ($P_{\text{corr}} = 0.001, K_E = 1290, T = 4.55$, peak co-ordinates = $-52, 18, -10$), a cluster with a peak in the right cerebellum ($P_{\text{corr}} = 0.007, K_E = 994, T = 4.27$, peak co-ordinates = $30, -88, -36$), a cluster centered on the left cerebellum ($P_{\text{corr}} < 0.001$,

$K_E = 1660$, $T = 5.30$, peak co-ordinates = $-28, -90, -34$). There were also significant clusters of activation (within the amygdala SVC) in control participants in the right amygdala ($P_{\text{corr}} = 0.029$, $K_E = 23$, $T = 3.96$, peak co-ordinates = $18, 2, -18$) and left amygdala ($P_{\text{corr}} = 0.035$, $K_E = 17$, $T = 3.50$, peak co-ordinates = $-22, -8, -20$).

Participants with schizophrenia, when taken as a group, showed activation in social brain regions within large clusters of activation centered on the left superior frontal gyrus (BA6; $P_{\text{corr}} < 0.001$, $K_E = 4359$, peak $T = 6.29$, peak co-ordinates = $-6, 8, 70$), right middle frontal gyrus (BA9; $P_{\text{corr}} < 0.001$, $K_E = 1811$, peak $T = 6.08$, peak co-ordinates = $56, 22, 22$), left inferior frontal gyrus (BA45; $P_{\text{corr}} < 0.001$, $K_E = 6248$, peak $T = 6.01$, peak co-ordinates = $-52, 24, -12$), and left supramarginal gyrus ($P_{\text{corr}} < 0.001$, $K_E = 1572$, peak $T = 5.46$, peak co-ordinates = $-58, -56, 36$). There were no significant clusters of activation within the amygdala SVC in the patient group.

Differences in BOLD Activation in Patients With Schizophrenia Compared With Control Participants

In the contrast of approachability judgments greater than gender judgments there was a relative overactivation in the individuals with schizophrenia vs controls in the right precuneus extending to right posterior cingulate cortex ($P_{\text{corr}} < 0.001$, $K_E = 3312$, peak $T = 5.04$, peak co-ordinates = $16, -66, 44$), middle frontal gyrus (BA9; $P_{\text{corr}} = 0.002$, $K_E = 1343$, peak $T = 4.69$, peak co-ordinates = $58, 26, 26$), and superior frontal gyrus (BA8; $P_{\text{corr}} = 0.029$, $K_E = 783$, peak $T = 4.51$, peak co-ordinates = $18, 22, 48$; [figure 1](#)). There were no significant activations in the reverse contrast, and there were no significant differences in the amygdala.

Amygdala Connectivity in Healthy Participants

Healthy participants demonstrated significant effective connectivity as assessed by PPI from the left amygdala to the left fusiform gyrus, extending over the cerebellum ($P_{\text{corr}} < 0.001$, $K_E = 1108$, peak $T = 5.76$, peak co-ordinates = $-36, -54, -14$), and to the right fusiform gyrus, extending over the cerebellum ($P_{\text{corr}} = 0.001$, $K_E = 887$, peak $T = 4.62$, peak co-ordinates = $40, -56, -24$; [figure 2](#)).

From the right amygdala, healthy participants showed significant effective connectivity to the right fusiform gyrus, extending to right cerebellum ($P_{\text{corr}} < 0.001$, $K_E = 2250$, peak $T = 6.11$, peak co-ordinates = $32, -46, -26$), and the inferior occipital gyrus/cuneus ($P_{\text{corr}} < 0.001$, $K_E = 1413$, peak $T = 6.33$, peak co-ordinates = $-16, -96, 0$; [figure 2](#)). They also showed significant effective connectivity from the right amygdala to the left superior frontal gyrus ($P_{\text{corr}} = 0.046$, $K_E = 424$, peak $T = 4.07$, peak co-ordinates = $-16, 34, 52$).

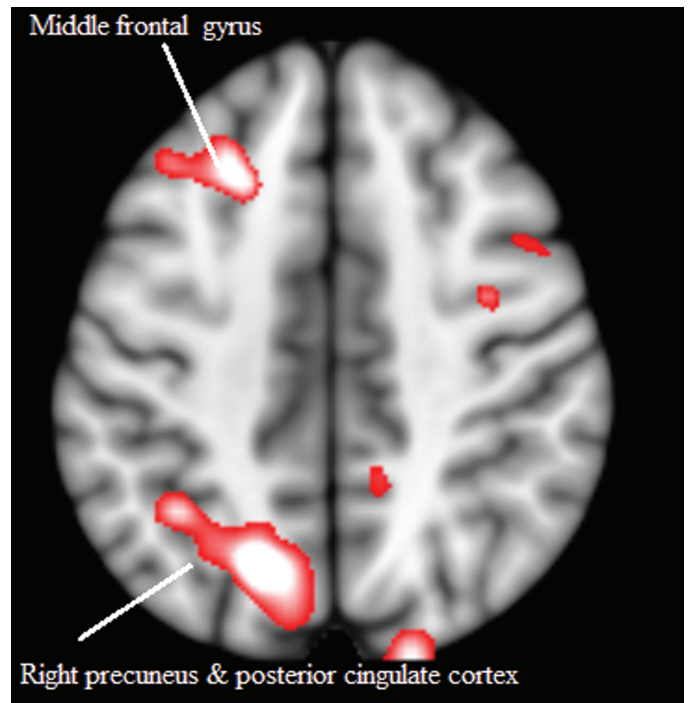


Fig. 1. Comparison of blood oxygen level-dependent activation in patients with schizophrenia and control subjects during approachability judgments. Greater activation of precuneus and middle frontal gyrus in the patient group.

Further, healthy participants showed evidence of connectivity from the bilateral amygdala to the right insula when the threshold was lowered ($P < .01$). For the connectivity from the left amygdala, the peak co-ordinates in the insula were (at $P < .01$, $K_E = 122$, peak $T = 4.20$, peak co-ordinates = $32, 3, -12$). For the connectivity from the right amygdala, the peak co-ordinates in the insula were (at $P < .01$, $K_E = 65$, peak $T = 4.21$, peak co-ordinates = $32, 2, -14$).

Reduced Connectivity in Individuals With Schizophrenia

Connectivity analysis in patients with schizophrenia showed no significant connectivity from either the left or the right amygdala. In direct comparison to controls, patients with schizophrenia showed a significant reduction in effective connectivity from the left amygdala to the right insula ($P_{\text{corr}} = 0.004$, $K_E = 802$, peak $T = 4.54$, peak co-ordinates = $34, 0, -6$; [figure 3](#)) and right hippocampus/parahippocampal gyrus ($P_{\text{corr}} = 0.042$, $K_E = 508$, peak $T = 3.89$, peak co-ordinates = $20, -12, -24$).

Individuals with schizophrenia showed significantly reduced connectivity from the right amygdala to the right insula compared with controls ($P_{\text{corr}} = 0.002$, $K_E = 958$, peak $T = 4.29$, peak co-ordinates = $34, 4, -10$; [figure 3](#)). No brain regions were found to have significantly higher amygdala connectivity in patients.

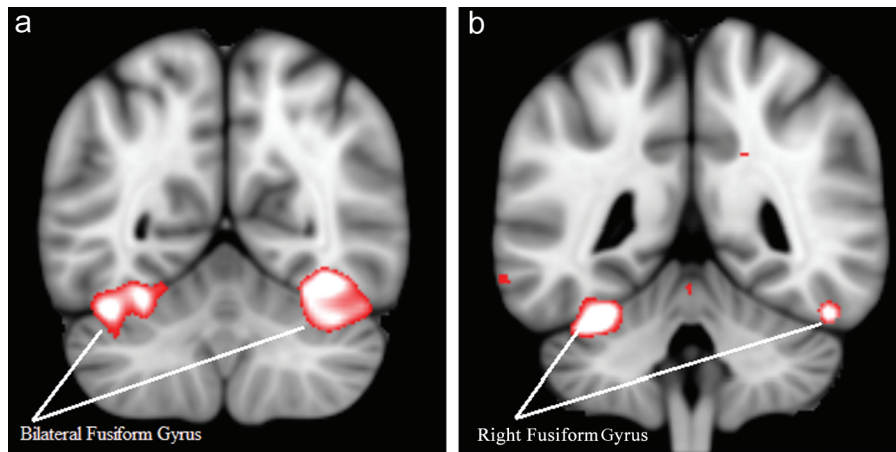


Fig. 2. Effective connectivity from the amygdala in healthy control participants during approachability judgments. Participants show effective connectivity between (a) left amygdala and fusiform gyrus/cerebellum and (b) right amygdala and fusiform gyrus/cerebellum.

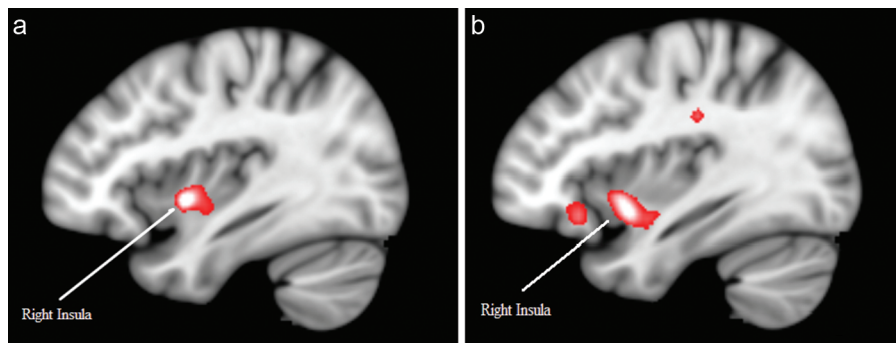


Fig. 3. Reduced connectivity from (a) left amygdala and (b) right amygdala to the right insula in patients compared with controls.

Correlation of Connectivity With Medication and Symptoms

No significant correlations were found between connectivity in patients and antipsychotic medication dosage or PANSS scores.

Discussion

Deciding whether to approach another individual is a critical social task and has been linked to a distributed brain network.^{11,50,57} Control subjects recruited key nodes within this network, including the fusiform gyrus, amygdala, cerebellum, and medial and inferior prefrontal cortex (extending to the insula).⁴⁹ Furthermore, they demonstrated expected patterns of connectivity between the amygdala and regions involved in processing sensory information from faces including the fusiform gyrus bilaterally.

In comparison to control participants, individuals with schizophrenia overactivated the superior frontal gyrus (BA8) and middle frontal gyrus (BA9, dorsolateral prefrontal cortex) when making judgments of approachability from faces. These are key brain regions involved in cognitive control. Both brain regions have frequently

been implicated in the pathology of schizophrenia by both structural and functional studies.⁵⁸⁻⁶⁰ Notably, previous studies have suggested that these regions may be linked to emotion regulation,⁶¹ and increased activation of regions, including the dorsolateral prefrontal cortex, has been demonstrated in patients with schizophrenia when greater emotional load impacts on cognitive processing.⁶² The greater activation of this cognitive network in patients with schizophrenia may therefore reflect a compensatory response to the joint cognitive and emotional demands of the social task.

Patients with schizophrenia also showed relative overactivation of the precuneus during social decision-making, compared with healthy controls. This brain region has been implicated in a range of cognitive functions including episodic memory retrieval, emotion processing, and the generation of self-related mental representations.^{63,64} The precuneus is also considered part of the default mode network of regions showing activity at rest, which may relate to its function in self-related representation.⁶⁴ Previous studies have shown overactivation of the precuneus during emotion processing and theory of mind judgments.^{65,66} The current finding of increased precuneus activation in patients with schizophrenia may therefore

reflect the recruitment of additional neural resources to accompany emotion processing and social judgments, and a corresponding failure to deactivate the default mode network, in patients compared with controls.

The amygdala plays a key role in social function,⁶⁷ is extensively connected to other parts of the brain¹⁹ and is a pivotal hub in social brain network.^{23,24} Abnormalities in the amygdala have been widely reported in schizophrenia,^{28,68} and amygdala dysfunction has been related to functional outcome in the disorder.⁶⁹ The reported amygdala abnormalities include reduced volume,^{27,28,58,70} abnormal functional activation patterns for social, emotion processing,²⁸ and altered connectivity.⁴⁵ We did not demonstrate changes in amygdala activation in patients with schizophrenia during approachability judgments, compared with gender judgments, in the current task. However, we did find evidence of altered connectivity between the amygdala and other brain regions involved in processing social and emotional information including the insula and the parahippocampal gyrus.

The insula is structurally and functionally connected to the amygdala, and the 2 regions play an interacting role in processing social and emotional information.^{11,20,71} Direct reciprocal connections have been demonstrated between the insula and most nuclei of the amygdala in rats,^{72,73} as well as in primates, including humans.^{20,74,75} Previous fMRI studies of social decision-making have shown conjoint activation of the amygdala and insula during social judgments including judgments of trustworthiness and approachability.^{50,57} The insula has been associated with assimilating interoceptive information of the internal body state giving rise to subjective emotion.⁷⁶ Further, it has also been suggested that the insula enables simulation of another individual's emotional state and may thus contribute to mentalization.⁷⁷⁻⁷⁹ Insula abnormalities have been previously reported in schizophrenia,⁶⁸ including reductions in volume,^{80,81} which some studies have also found, to be correlated with positive symptoms.^{68,82} Abnormal functional activation of the amygdala has also been reported in schizophrenia, particularly during the processing of emotional information from faces.⁶⁸ Together, these indications of abnormality in the amygdala and insula in schizophrenia, along with their high degree of interconnectedness and closely related functionality in social and emotion processing, suggest that reduced connectivity between these regions may contribute to the observed deficits in social and emotional function seen in the disorder.

Patients with schizophrenia also showed reduced amygdala connectivity to the hippocampus and the parahippocampal gyrus (PHG). These regions are linked to memory functions, which are important for processing stimuli in relation of previous knowledge and experience.⁸³⁻⁸⁵ Both volume deficits^{86,87} and functional abnormalities^{88,89} have been reported for these regions in schizophrenia. Neuropathological findings for the hippocampus in

schizophrenia are associated with neuronal morphology and presynaptic and dendritic parameters, which are factors linked to functional connectivity.⁸⁸ In the context of these previous findings, the results presented here support the view that dysconnectivity between the amygdala and hippocampus and PHG may contribute to the social behavior deficits seen in schizophrenia.

Functional dysconnectivity has been previously reported in schizophrenia for a range of other brain functions, including working memory,⁹⁰ language,³⁴ and emotion processing.^{31,38,44} Several of these are reviewed in Brown and Thompson.⁹¹ Indeed, functional disconnection has been implicated as a core pathological factor in the disorder.²⁹ We believe that decreased connectivity between core components of the emotional and social brain network, such as the amygdala and insula, may contribute to the observed impairments in social cognition seen in this disorder. Furthermore, we hypothesize that the over-recruitment of regions involved in cognitive control (such as the dorsolateral prefrontal cortex) and areas of association cortex (such as the precuneus) may represent a form of function compensation in the context of impaired emotion processing ability. Notably, we did not see differences in task performance in the scanner in this study. This might be because patients were able to overcome the effects of the disconnection in this relatively low-demand social task by increased activation of other regions including areas involved in higher cognitive function such as the dorsolateral prefrontal cortex. Future work could use more challenging tasks of emotional regulation for social judgment to investigate how this socioemotional network responds to increases in task load.

Some limitations to this study should be noted. First, all the patients in the study were medicated, and many had significant symptoms at the time of scanning. However, we found no specific correlation between medication dose or symptom ratings and connectivity in this study. In addition, we specifically focussed on connectivity from the amygdala and did not examine connectivity from seeds in other brain regions. However, the amygdala is a major hub in the social brain activated by the current task, and by focussing on this theoretically important region, we were able to reduce issues associated with multiple hypothesis testing across many brain regions.

In conclusion, we show that when making social judgments of approachability, individuals with schizophrenia have reduced effective connectivity between the amygdala and the insula, another key brain region involved in social and emotional processing. In addition, we show concurrent increased activation of frontal brain regions involved in cognitive control and of parietal association cortex in patients performing this task. We suggest that these areas of increased activation in patients with schizophrenia may in part represent compensation for impaired functional integration of the social brain network in the disorder.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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